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<p>(54) Title: PHARMACEUTICAL COMPOSITION</p> <p>(57) Abstract</p> <p>This invention relates to a pharmaceutical composition for oral administration comprising a carrier and, as an active ingredient, a 5-HT₁ agonist, characterised in that the composition is formulated to reduce pre-systemic metabolism of said 5-HT₁ agonist. A process for preparing such a composition and the use of such a composition for the treatment of anxiety, depression, attention deficit disorder and/or panic disorders and/or as a memory enhancer are also provided.</p>			

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PHARMACEUTICAL COMPOSITION

This invention relates to a pharmaceutical
5 composition, a process for preparing such a composition
and the use of such a composition for the treatment of
anxiety, depression, attention deficit disorder and/or
panic disorders, sleep apnoea and/or related respiratory
disorders and/or substance addiction, especially alcohol
10 abuse, the treatment and/or prophylaxis of incontinence
disorders, inducing immunosuppression and/or treating
immune disorders, the alleviation of extrapyramidal motor
disorders and/or as a memory enhancer.

Buspirone (8-[4-[4-(2-pyrimidinyl)-1-
15 piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione) has
been shown to be effective in the treatment of anxiety.
The mechanism of action of buspirone has not been fully
elucidated. However, it is known that buspirone is a 5-
HT₁ agonist and, in particular, a potent 5-HT_{1A} agonist
20 and it is thought that it is action at these receptors
which may account for its anxiolytic activity.

Buspirone is currently administered orally in the
form of a conventional tablet which is scored in a manner
which provides for it to be broken into halves or thirds
25 along breaklines, thus allowing for some titration of the
dose. However, each tablet or portion thereof is
designed to be swallowed whole. Doses range from 15 to
60 mg per day and may be delivered as 2 or 3 divided
doses. When administered in this way, buspirone is
30 absorbed from the gastrointestinal tract, that is, the
stomach, the small intestine and the proximal large
intestine (colon), into the hepatic portal system and is
presented to the liver before reaching the systemic
circulation. The liver is known to be the principal site
35 for conversion of active buspirone into metabolites and,
indeed, buspirone is rapidly metabolised by the liver
into a large number of metabolites. In a radio-label

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study in man, twelve metabolites of buspirone were isolated from urine (see H. K. Jajoo et al, Drug Metabolism and Disposition, (1989), 17, 634-640). However, only one of these metabolites, 1-pyrimidinylpiperazine (1-PP), has been reported to possess any potential therapeutic activity and this compound is said to possess, at most, only 20% of the activity of unchanged buspirone as determined by the Vogel conflict test in rats (see R.E. Gammans et al, Am.J.Med., (1986), 80(suppl.3B), 41-51).

The mean systemic availability of unchanged buspirone is thought to be about 4% after conventional oral administration and the plasma levels of this drug are said to exhibit great variability. This latter effect has been attributed to differences between individuals in pre-systemic metabolism, that is, metabolism in the gastrointestinal tract, in the membranes lining the gastrointestinal tract and also in the liver. However, it is clear that the clinical effectiveness of buspirone is compromised by the extensive pre-systemic metabolism of this drug which occurs following conventional oral administration.

Buspirone is an example from a class of compounds known as the azapirones which have been shown to be effective in the treatment of anxiety. Other azapirones include 4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2,6-piperidinedione (gepirone), 2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (ipsapirone), (3a α ,4 α ,4a β ,6a β ,7 α ,7a α)-3a,4,4a,6a,7,7a-hexahydro-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-4,7-etheno-1H-cyclobut[f]isoindole-1,3(2H)-dione (zalospirone), 3-butyl-7-[4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl]-9,9-dimethyl-3,7-diazabicyclo[3.3.1]nonane-2,4,6,8-tetron (umespirone), (S)-8-[4-[(3,4-dihydro-5-methoxy-2H-1-benzopyran-3-yl)propylamino]butyl]-8-azaspiro[4.5]decane-7,9-dione (alnespirone), 6-(3-

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chlorophenoxy)-2-methyl-1-oxa-4-azaspiro[4.5]decan-3-one
(enilospirone), octahydro-3-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-1,5-methano-6,7,9-metheno-1H-pentaleno[1,2-d]azepine-2,4(3H,5H)-dione (WY-48723), 4-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-1,4-benzoxazepine-3,5(2H,4H)-dione (SUN-8399), (3a α ,4 β ,7 β ,7a α)-hexahydro-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-4,7-methano-1H-isoindole-1,3(2H)-dione 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (tandospirone) and salts thereof. All these compounds act as agonists at 5-HT₁ receptors, particularly 5-HT_{1A} receptors, and, like buspirone, are subject to extensive pre-systemic metabolism. Other compounds which interact with 5-HT₁ receptors (5-HT₁ agonists) include
(+)-N-[2-[4-[2,3-dihydro-2-(hydroxymethyl)-1,4-benzodioxin-5-yl]-1-piperazinyl]ethyl]-4-fluorobenzamide (flesinoxan), 2-[4-[4-(4-chloro-1H-pyrazol-1-yl)butyl]-1-piperazinyl]pyrimidine (lesopitron), (R)-3,4-dihydro-N-(1-methylethyl)-3-((1-methylethyl)propylamino)-2H-1-benzopyran-5-carboxamide (ebalzotan), N-[2-[4-(2-pyrimidinyl)-1-piperazinyl]]adamantane-1-carboxamide (adatanserin), (R)-4-(dipropylamino)-1,3,4,5-tetrahydro-benz(cd)indole-6-carboxamide (LY-228729), F-8910-RS, (-)-cis-3-propyl-2,3,3a(R),4,5,9b-hexahydro-14-benz[e]indole-9-carboxamide (U-93385), 4-[2-[4-(naphthalen-1-yl)piperazin-1-yl]ethyl]quinolin-2(1H)one (SL-87.0765), 2-[4-[4,4-bis(4-fluorophenyl)butyl]-1-piperazinyl-3-pyridinecarboxylic acid methyl ester (FG-5893), 4-fluoro-N-[2-[4-[7-methoxy-1-naphthyl]piperazin-1-yl]ethyl]benzamide (S-14506), 5-methoxy-3-[4-(4-(4-methoxyphenyl)-1-piperazinyl)butyl]indole (EMD-56551), (-)-N-[2-(8-methyl-1,4-benzodioxan-2-ylmethylamino)ethyl]adamantane-1-carboxamide (HT-90B), F-92502-CN, 2-[4-[4-(4-nitropyrazol-1-yl)butyl]piperazin-1-yl]pyrimidine (E-4414), 5-[3-[(2S)-1,4-benzodioxan-2-ylmethyl]-amino]propoxy]-1,3-benzodioxolane (MKC-242), 4-methyl-2-

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[4- (4- (pyrimidin-2-yl) -piperazino)butyl]-2H, 4H-1, 2, 4-triazin-3, 5-dione (F-12439), 1-(2-(4-(3-trifluoromethylphenyl)piperazin-1-yl)ethyl)benzimidazol-[1H]-2-one (BIMT-17), LY-39, SL-88.0338, 1, 2, 3, 6-
5 tetrahydro-1-[2-(2-naphthalenyl)ethyl]-4-[3-(trifluoromethyl)phenyl]pyridine (SR-57746A), 1-(9H-fluoren-2-yl)-2-(1H-imidazol-1-yl)ethanone (LY-175644), (+/-)trans-2-(4-(3a, 4, 4a, 6a, 7, 7a-hexahydro-4, 7-etheno-1H-cyclobut [f]isoindol-1, 3-dionyl)butyl-9-methoxy-
10 2, 3, 3a, 4, 5, 9b-hexahydro-1H-benz[e]isoindole (A-74283), 1, 3, 4, 5-tetrahydro-6-methoxy-N,N-dipropylbenz[cd]indol-4-amine (Bay-r-1531), 4-(4-methyl-1-piperazinyl)-7-(trifluoromethyl)-pyrrolo[1, 2-a]quinoxaline (Z)-2-butenedioate (1:2) (CGS-12066B), trans-1, 3, 4, 4a, 5, 10b-
15 hexahydro-10-methoxy-4-propyl-2H-[1]benzopyrano[3, 4-b]pyridine (CGP-50281), N-propyl-N-[2-(4-fluorobenzamido)ethyl]amino-5, 6, 7, 8-tetrahydroquinoline (WAY-100012), 3a, 4, 4a, 6a, 7, 7a-hexahydro-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-4, 7-ethenocyclobuta[f]-
20 1, 2-benzisothiazol-3(2H)-one 1, 1-dioxide, cis-7-chloro-10-methoxy-5a, 10b-dihydro-3N-n-propyl-6H-indeno[1, 2-d]azepine, 1-cyclohexyl-3-[4-[4-(2, 3-dihydro-2, 2-dimethylbenzofuran-7-yl)-1-piperazinyl]-1-butyl]-2-imidazolidinone, 1-[3-amino-2H-1-benzopyran-2-one-8-
25 yl)piperazine, 4-(1-methylethyl)-2-[3-(trifluoromethyl)-phenyl]morpholine (oxaflozane), N, 5-dimethyl-10-dibenz-(b, f)azepine-ethanamine (RU-5031), 1, 4-dihydro-3-(1, 2, 3, 6-tetrahydro-4-pyridinyl)-5H-pyrrolo[3, 2-b]-pyridin-5-one (CP-93129), N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide
30 (naratriptan), 3-[3-[4-(5-methoxy-4-pyrimidinyl)-1-piperazinyl]propyl]-N-methyl-1H-indole-5-methanesulphonamide (avitriptan), N, N-dimethyl-5-(1H-1, 2, 4-triazol-1-ylmethyl)-1H-indole-3-ethanamine
35 (rizatriptan), N-[4-[[5-[3-(2-aminoethyl)-1H-indol-5-yl]-1, 2, 4-oxadiazol-3-yl]methyl]phenyl]methanesulphonamide (L-694247), IS-159, 1-(((3-(2-(dimethylamino)ethyl)-1H-

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indol-5-yl)methyl)sulphonyl)pyrrolidine (almotriptan),
4-((3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)methyl)-(S)-
2-oxazolidinone (zolmitriptan), 3-[2-(dimethylamino)-
ethyl]-N-methyl-1H-indole-5-methanesulphonamide
5 (sumatriptan), 3-((1-methyl-2-pyrrolidinyl)methyl)-5-(2-
(phenylsulphonyl)ethyl)-(R)-1H-indole (eletriptan),
(R)-(+)-3-(methylamino)-1,2,3,4-tetrahydro-9H-carbazole-
6-carboxamide (VML-251), L-0076, ALX-0625,
10 (R)-N-methyl-[3-(1-methyl-2-pyrrolidinyl)-1H-indol-5-
yl]methanesulphonamide (CP-122288), 3-[3-[4-(5,6-
dimethoxypyrimidin-4-yl)piperazin-1-yl]propyl]-N-methyl-
1H-indol-5-yl-methanesulphonamide (VS-395), L-747201,
LY-334370 and salts thereof.

It would be highly desirable from a clinical
15 point of view to find a way of administering such 5-HT₁
agonists so that the bioavailability of the active
ingredient is enhanced and the variability in plasma
levels caused by differences in pre-systemic metabolism
is reduced.

20 According to the present invention there is
therefore provided a pharmaceutical composition for oral
administration comprising a carrier and, as an active
ingredient, a 5-HT₁ agonist, characterised in that the
composition is formulated to reduce pre-systemic
25 metabolism of the 5-HT₁ agonist.

If pre-systemic metabolism of the active
ingredient is to be reduced, it is important that the
active ingredient is absorbed into the systemic
circulation at a site which enables the active ingredient
30 to avoid entering the portal circulation to the liver and
thus avoid extensive metabolism by the liver (the so-
called "first pass effect"). Since absorption from the
gastrointestinal tract is known to result in the active
ingredient entering the hepatic portal system to the
35 liver, one option for reduction of pre-systemic
metabolism is to promote absorption from sites before the
active ingredient reaches the gastrointestinal tract.

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Accordingly, it is preferred that the composition of the invention is formulated to promote pre-gastric absorption of the 5-HT₁ agonist.

The term "pre-gastric absorption" is used to
5 refer to absorption of the active ingredient from that part of the alimentary canal prior to the stomach and includes buccal, sublingual, oropharyngeal and oesophageal absorption.

It is envisaged that such pre-gastric absorption
10 will occur primarily across the mucous membranes in the mouth, pharynx and oesophagus. Accordingly, it is preferred that the composition of the invention is formulated to promote absorption of the active ingredient through the buccal, sublingual, pharyngeal and/or
15 oesophageal mucous membranes.

It is therefore preferred that the composition of the invention should be in a form which sustains the active ingredient in contact with the buccal, sublingual, pharyngeal and/or oesophageal mucous membranes.

20 Preferably, the composition of the invention is in the form of a viscous emulsion, syrup or elixir, a sub-lingual tablet, a suckable or chewable tablet, softgel, lozenge, aqueous or non-aqueous drops or other dosage form designed to release the active ingredient in
25 a controlled manner to saliva or to the buccal, pharyngeal and/or oesophageal mucous membranes, a fast-dispersing dosage form designed rapidly to release the active ingredient in the oral cavity, or a bioadherent system.

30 The term "bioadherent system" refers to a solid or liquid dosage form which, at body temperature, exhibits controlled release and bioadherence characteristics. This type of dosage form may be an emulsion which is water in oil in nature and whose
35 internal phase is greater than that of the external phase. Examples of such bioadherent systems may be found in U.S. Patent No. 5055303.

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Of the dosage forms listed above, fast-dispersing dosage forms are particularly preferred since they will disintegrate rapidly in the mouth without the need for water, or other liquid, to aid swallowing. Such fast-dispersing dosage forms are therefore more convenient and easier for patients to take than conventional oral dosage forms. Also, since no water, or other liquid, is required to take such fast-dispersing dosage forms, the active ingredient is presented for absorption at a higher concentration than with conventional oral dosage forms. Thus, use of such fast-dispersing dosage forms may allow a reduction in the dose required to achieve the desired therapeutic effect which, in turn, may result in a reduction in the incidence and/or severity of side effects. More reproducible plasma levels of the active ingredient may also be achieved with such dosage forms.

Since such fast-dispersing dosage forms produce a concentrated solution of the active ingredients in the saliva of the mouth, it is also possible that, when swallowed, this concentrated solution coats the stomach mucosa more effectively than a conventional drug dissolved in water and this may increase the rate of absorption of the active ingredient. Moreover, absorption from the highest part of the stomach may also by-pass the hepatic portal vein and hence produce a higher level of the active ingredient in the plasma.

One example of a fast-dispersing dosage form is described in U.S. Patent No. 4855326 in which a melt spinnable carrier agent, such as sugar, is combined with an active ingredient and the resulting mixture spun into a "candy-floss" preparation. The spun "candy-floss" product is then compressed into a rapidly dispersing, highly porous solid dosage form.

U.S. Patent No. 5120549 discloses a fast-dispersing matrix system which is prepared by first solidifying a matrix-forming system dispersed in a first solvent and subsequently contacting the solidified matrix

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- with a second solvent that is substantially miscible with the first solvent at a temperature lower than the solidification point of the first solvent, the matrix-forming elements and active ingredient being
5 substantially insoluble in the second solvent, whereby the first solvent is substantially removed resulting in a fast-dispersing matrix.

U.S. Patent No. 5079018 discloses a fast-dispersing dosage form which comprises a porous skeletal structure of a water soluble, hydratable gel or foam forming material that has been hydrated with water, rigidified in the hydrated state with a rigidifying agent and dehydrated with a liquid organic solvent at a temperature of about 0°C or below to leave spaces in place
15 of hydration liquid.

Published International Application No. WO 93/12769 (PCT/JP93/01631) describes fast-dispersing dosage forms of very low density formed by gelling, with agar, aqueous systems containing the matrix-forming
20 elements and active ingredient, and then removing water by forced air or vacuum drying.

U.S. Patent No. 5298261 discloses fast-dispersing dosage forms which comprise a partially collapsed matrix network that has been vacuum-dried above the collapse
25 temperature of the matrix. However, the matrix is preferably at least partially dried below the equilibrium freezing point of the matrix.

Published International Application No. WO 91/04757 (PCT/US90/05206) discloses fast-dispersing dosage forms which contain an effervescent disintegration agent designed to effervesce on contact with saliva to provide rapid disintegration of the dosage form and dispersion of the active ingredient in the oral cavity.
30

U.S. Patent No. 5595761 discloses a particulate support matrix for use in making a rapidly dissolving tablet, comprising;
35 a first polypeptide component having a net charge

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when in solution, e.g. non-hydrolysed gelatin;
a second polypeptide component having a net
charge of the same sign as the net charge of the first
polypeptide component when in solution e.g. hydrolysed
5 gelatin; and
a bulking agent, and wherein the first
polypeptide component and the second polypeptide
component together comprise about 2% to 20% by weight of
the particulate support matrix and wherein the bulking
10 agent comprises about 60% to 96% by weight of the
particulate support matrix; and
wherein the second polypeptide component has a
solubility in aqueous solution greater than that of the
first polypeptide component and wherein the mass: mass
15 ratio of the first polypeptide component to the second
polypeptide component is from about 2 : 1 to about 1 :
14; and
wherein when the support matrix is introduced
into an aqueous environment the support matrix is
20 disintegrable within less than about 20 seconds.
US Patent No. 5576014 discloses fast-dispersing
dosage forms which dissolve intrabuccally and which
comprise compressed moldings formed from granules
comprising a saccharide having low moldability which has
25 been granulated with a saccharide having high
moldability. The resulting compressed moldings show
quick disintegration in the buccal cavity.
EP-B-0690747 describes particles comprising an
excipient forming a matrix and at least one active
30 ingredient uniformly distributed in the mass of the
matrix which are prepared by a process comprising the
steps of preparing an homogeneous pasty mixture with a
viscosity below 1 Pa.s, measured at room temperature (15-
20°C), from at least one active ingredient, a
35 physiologically acceptable hydrophilic excipient and
water; extruding the resulting homogeneous mixture and
cutting the extrudate to give moist particles; freezing

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the resulting particles as they fall under gravity through a stream of inert gas at a temperature below 0°C; and drying the particles by freeze drying.

Australian Patent No. 666666 discloses a rapidly 5 disintegratable multiparticulate tablet having a mixture of excipients in which the active substance is present in the form of coated microcrystals or optionally coated microgranules. Such tablets disintegrate in the mouth in an extremely short time, typically less than 60 seconds.

US Patent No. 5382437 discloses a porous carrier 10 material having sufficient rigidity for carrying and administering an active material which is capable of rapid dissolution by saliva and which is formed by freezing a liquefied ammonia solution comprising liquid 15 ammonia, a liquid ammonia-soluble gel or foam material and a rigidifying agent for the gel or foam material selected from the group consisting of a monosaccharide, a polysaccharide and combinations thereof, and deammoniating the frozen material thus formed by causing 20 material transfer of ammonia from the frozen state to the gas state thereby leaving spaces in the carrier material in place of the frozen ammonia.

Published International Application No. WO 25 93/13758 (PCT/US92/07497) describes tablets of increased physical strength which are prepared by combining and compressing a melttable binder, excipients and a pharmaceutically active agent into a tablet, melting the binder in the tablet and then solidifying the binder. In one embodiment, a disintegrating agent is utilised to 30 increase the disintegration rate of the tablet after oral intake. In another embodiment, a volatilisable component is used to form porous tablets. Some embodiments disintegrate in the mouth in less than 10 seconds.

US Patents Nos. 3885026 and 4134943 also disclose 35 fast-dispersing porous tablets and a method for increasing their physical strength by first compressing the tablet and then volatilising a readily volatilisable

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solid adjuvant incorporated in the tablet to attain the desired porosity.

EP-A-0601965 describes a shearform matrix material which can be used, inter alia, to deliver a pharmaceutically active agent. The shearform matrix is formed by increasing the temperature of a feedstock which includes a solid non-solubilised carrier material to the point where it will undergo internal flow with the application of a fluid shear force, ejecting a stream of the heated feedstock thus formed under pressure from an orifice and then subjecting the feedstock to disruptive fluid shear force which separates the flow of feedstock into multiple parts and transforms the morphology of the feedstock.

US Patent No. 5683720 discloses discrete particles containing a pharmaceutically active agent which can be fast-dispersing and are formed by subjecting a solid, organic feedstock to liquiflash conditions whereby the feedstock is transformed instantaneously from solid to liquiform to solid, liquiform being a transient condition in which the feedstock has substantially unimpeded internal flow. Shear force is then imparted to the liquiform feedstock in an amount sufficient to separate tiny masses of feedstock which then solidify as discrete particles.

The term "fast-dispersing dosage form" therefore encompasses, but is not limited to, all the types of dosage form described in the preceding paragraphs. However, it is particularly preferred that the fast-dispersing dosage form is of the type described in U.K. Patent No. 1548022, that is, a solid fast-dispersing dosage form comprising a network of the active ingredient and a water-soluble or water-dispersible carrier which is inert towards the active ingredient, the network having been obtained by subliming solvent from a composition in the solid state, that composition comprising the active ingredient and a solution of the carrier in a solvent.

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It is preferred that the composition of the invention disintegrates within 1 to 60 seconds, more preferably 1 to 30 seconds, especially 1 to 10 seconds, and particularly 2 to 8 seconds, of being placed in the
5 oral cavity.

In the case of the preferred type of fast-dispersing dosage form described above, the composition will preferably contain, in addition to the active ingredient, matrix forming agents and secondary
10 components. Matrix forming agents suitable for use in the present invention include materials derived from animal or vegetable proteins, such as the gelatins, dextrins and soy, wheat and psyllium seed proteins; gums such as acacia, guar, agar, and xanthan; polysaccharides;
15 alginates; carboxymethylcelluloses; carrageenans; dextrans; pectins; synthetic polymers such as polyvinylpyrrolidone; and polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes.

20 Other matrix forming agents suitable for use in the present invention include sugars such as mannitol, dextrose, lactose, galactose and trehalose; cyclic sugars such as cyclodextrin; inorganic salts such as sodium phosphate, sodium chloride and aluminium silicates; and
25 amino acids having from 2 to 12 carbon atoms such as a glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine.

One or more matrix forming agents may be
30 incorporated into the solution or suspension prior to solidification. The matrix forming agent may be present in addition to a surfactant or to the exclusion of a surfactant. In addition to forming the matrix, the matrix forming agent may aid in maintaining the dispersion of any active ingredient within the solution or suspension. This is especially helpful in the case of active agents that are not sufficiently soluble in water
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and must, therefore, be suspended rather than dissolved.

Secondary components such as preservatives, antioxidants, surfactants, viscosity enhancers, colouring agents, flavouring agents, pH modifiers, sweeteners or taste-masking agents may also be incorporated into the composition. Suitable colouring agents include red, black and yellow iron oxides and FD & C dyes such as FD & C blue No. 2 and FD & C red No. 40 available from Ellis & Everard. Suitable flavouring agents include mint, raspberry, liquorice, orange, lemon, grapefruit, caramel, vanilla, cherry and grape flavours and combinations of these. Suitable pH modifiers include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Suitable sweeteners include aspartame, acesulfame K and thaumatin. Suitable taste-masking agents include sodium bicarbonate, ion-exchange resins, cyclodextrin inclusion compounds, adsorbates or microencapsulated actives.

Preferred compositions in accordance with this invention include a 5-HT_{1A} agonist, especially an azapirone or a salt thereof, as the active 5-HT₁ agonist. It is particularly preferred that the active 5-HT₁ agonist is buspirone or a salt thereof.

Buspirone which is absorbed by pre-gastric absorption or at a high rate across the stomach mucosa from a composition in accordance with this invention passes straight into the systemic circulatory system thereby avoiding first pass metabolism in the liver. Accordingly, the initial rapid production of unwanted, inactive metabolites is reduced and the bioavailability of active buspirone is increased. This results in a number of advantages. For instance, the increased bioavailability of active buspirone means that the dose of buspirone may be reduced whilst still producing the desired beneficial effect. This will result in a further decrease in the production of unwanted metabolites and a reduction in the incidence and/or severity of side

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effects.

In the case of buspirone, the active ingredient preferably is present in the composition in an amount of from 0.5 to 30%, more preferably 1 to 20%, by weight of
5 the composition. It is also preferred that the active ingredient is present in the composition in an amount of from 0.25 to 50 mg, more preferably 0.5 to 10 mg and, especially, 1 to 10 mg.

In the case of other 5-HT₁ agonists, these also
10 will be present in concentrations which are clinically effective.

According to another aspect of the invention there is provided a process for preparing a pharmaceutical composition as defined above which
15 comprises bringing a carrier into association with the active ingredient.

In a further aspect, the invention provides the use of a fast-dispersing dosage form designed to release active ingredient rapidly in the oral cavity to deliver a
20 5-HT₁ agonist. A method of administering a 5-HT₁ agonist to a patient which comprises introducing into the oral cavity of the patient a composition as previously defined is also provided.

The invention also provides, in another aspect, a composition as defined above for use in the treatment of anxiety. The composition of the invention is also useful
25 in the palliative treatment of anxiety neurosis, that is, neurosis with a preponderance of anxiety symptoms.

5-HT₁ agonists, especially the azapirones, have
30 also been evaluated in the treatment of depression, attention deficit disorder and panic disorders and as memory enhancers. Also, the azapirones, especially buspirone, have been found to be useful in the treatment and/or prophylaxis of incontinence disorders associated
35 with the gastrointestinal or urogenital tracts, such as urinary incontinence, faecal incontinence and urinary retention. Such compounds are also useful for inducing

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immunosuppression and/or treating immune disorders and are therefore useful in the treatment of conditions such as contact, atopic or eczematous dermatitis and Sjogren's syndrome (including secondary keratoconjunctivitis sicca), autoimmune diseases and diseases of known or unknown etiology having an immunological component or allergies, especially rheumatoid arthritis and, in particular, juvenile rheumatoid arthritis. Such compounds may also be used in the treatment of sleep apnoea and related respiratory disorders, such as sudden infant death syndrome, and can also alleviate the symptoms of sleep apnoea such as anxiety, depression, fatigue, malaise, irritability, anger and hostility.

In addition, azapirones such as buspirone can be used in the treatment of substance addiction. In this respect, substance addiction includes over-eating, eating disorders and the habitual use of alcohol, tobacco, marijuana, cocaine, opiates, methadone, amphetamine, methphenidate and related designer drugs. Such compounds are particularly useful in the treatment of alcohol abuse as they also reduce the craving for alcohol and can therefore be used for treating patients undergoing short term treatment of alcohol withdrawal and in chronic alcohol abusers. Use of such compounds in the treatment of alcohol abuse avoids the enhancement or continuation of sensory impairment, the risk of developing drug dependence and the unpleasant effects of so-called aversion therapy. Moreover, such compounds produce behavioural modifications which include lessening of alcohol craving and ingestion and improvement of social functioning. In addition, psychogenic symptoms, such as illness, anxiety, depression, clouded sensorium, hostility, violence and decreased cognition, are alleviated.

Azapirones, particularly buspirone, are also useful for the alleviation of extrapyramidal motor disorders and can therefore be used to treat such

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conditions as Parkinson's disease, neuroleptic-induced extrapyramidal symptoms and tardive dyskinesia.

In addition to the above conditions, 5-HT₁ agonists have also been used in the treatment of social phobia, obsessive-compulsive disorder, migraine, cerebellar ataxia, levodopa-induced dyskinesias, Huntington's disease, central and peripheral neurodegenerative disorders, emesis, hypertension, hayfever, asthma and pruritis and to assist smokers in giving up smoking.

Of the 5-HT₁ agonists other than the azapirones, the 5-HT_{1D} agonists have been found to be especially useful in the treatment of migraine and related conditions.

According to a further aspect of the invention there is therefore provided the use of a composition as defined above for the manufacture of a medicament for the treatment of depression, attention deficit disorder, panic disorders, sleep apnoea and/or related respiratory disorders and/or substance addiction, especially alcohol abuse, the treatment and/or prophylaxis of incontinence disorders, inducing immunosuppression and/or treating immune disorders, the alleviation of extrapyramidal motor disorders and/or as a memory enhancer.

This invention is further illustrated by the following examples.

Example 1.

Preparation of a fast-dispersing dosage form of buspirone hydrochloride

(a) Preparation of buspirone hydrochloride 2.0% dispersion

Gelatin (720g) and mannitol (540g) were dispersed in a portion of purified water (16kg) by mixing thoroughly in the bowl of a vacuum mixer. The mix was then heated to 40°C ± 2°C and homogenised for ten minutes. The mix was

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cooled down to room temperature (20-24°C). When cooled the glycine (180g) and buspirone hydrochloride (360g) was added. The mix was homogenised to ensure dissolution of glycine and the drug. Citric acid (54g) was added 5 gradually with stirring, to adjust the solution pH to 4.0. The remaining water (146g) was added to the mixer and the bulk mix homogenised to ensure dissolution was complete.

(b) Preparation of buspirone hydrochloride 10mg units
10 500mg of the buspirone hydrochloride 2.0% dispersion formed in (a) above was dosed into each one of a series of pre-formed blister pockets having a pocket diameter of 16mm. The blister laminate comprised 200µm PVC coated with 40gsm PVdC. The product was frozen immediately in 15 a liquid nitrogen freeze tunnel. The frozen product was then stored below -18°C for a minimum of 40 hours prior to freeze-drying in a freeze drier using a drying temperature of +20°C and a chamber pressure of 0.5 mbar. The freeze dried units were then inspected for the 20 presence of critical defects and the remainder of the batch sealed with lidding foil consisting of a paper/foil laminate (20µm aluminium).

Each blister was then coded with a batch number and overwrapped in a preformed sachet by placing the 25 blister in the sachet and sealing the open end of the sachet completely. Each sachet was then labelled with the product name, batch number, date of manufacture and suppliers name.

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Each dosage unit had the following composition:

	Ingredient	Weight (mg)	% by wt of composition
5	Purified Water USP/EP*	448.500	89.7
	Buspirone HC1 USP	10.000	2.0
	Gelatin EP/USNF	20.000	4.0
	Mannitol EP/USP	15.000	3.0
	Glycine USP	5.000	1.0
	Citric Acid	1.500	0.3
Total		500.000	100.000

*Signifies removed during the lyophilisation process.

15 Example 2

Comparative pharmacokinetic study

The aim of this experiment was to compare the bioavailability of the buspirone hydrochloride formulation of Example 1 with the commercially available tablet formulation of buspirone hydrochloride sold under the registered Trade Mark "Buspar" by Bristol-Myers Pharmaceuticals, Bristol-Myers Squibb House, 141-149 Staines Road, Hounslow, Middlesex, TW3 3JA, England.

An open label, randomised, crossover, volunteer study was performed as follows. Six fasted, healthy male subjects of ages between 18 and 40 years, giving written informed consent, underwent a thorough medical examination to establish their fitness to participate in the study. Subjects received study treatment in the order dictated by a pre-determined randomisation schedule. Subjects were given either the formulation of Example 1 or the "Buspar" formulation. Blood samples for determination of pharmacokinetic parameters were taken at baseline (immediately before drug administration), then after 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 12 and 24 hours. The study procedures were repeated two weeks later, when subjects were crossed-over to receive

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their second drug administration. Buspirone hydrochloride was administered as single 20 mg doses (made up from 2 x 10 mg tablets) of the formulation of Example 1 or of the "Buspar" formulation.

5 HPLC-MS assays were performed to determine the concentration of buspirone and 1-pyrimidinylpiperazine (1-PP) in each of the blood plasma samples. The following pharmacokinetic parameters were determined for both analysed substances: bioavailability (as measured
10 as the area under the curve (AUC) of the drug concentration/time plot) and C_{max} (the maximum plasma concentration achieved).

15 The results are shown in graphical form in Figures 1 and 2 where each figure is a plot of the concentration of a specific compound in a blood plasma sample versus the time at which the sample was taken for the formulation of Example 1 (Example 1) and the tablet formulation sold under the registered Trade Mark "Buspar" (Buspar). In Figure 1, the specific compound is
20 buspirone. In Figure 2, the specific compound is 1-pyrimidinylpiperazine (1-PP).

The mean results are shown in numerical form in Table 1 below.

25 TABLE 1

	Buspirone C _{max} (ng/ml)	AUC _(0-24hr) (ng/ml.hr)	1-PP C _{max} (ng/ml)	AUC _(0-24hr) (ng/ml.hr)
Example 1, 20 mg	13.0	33.4	6.5	46.5
Buspar 20mg	3.6	8.0	6.8	37.9

30

From Figures 1 and 2 and Table 1, it is apparent that the bioavailability of buspirone from the formulation of Example 1 is about four times that of
35 buspirone from the "Buspar" formulation despite the fact that both formulations contained the same amount of

-20-

active ingredient. Also, the bioavailability of 1-pyrimidinylpiperazine (1-PP) is very similar for both formulations. However, in view of the much greater bioavailability of buspirone from the formulation of
5 Example 1, it is envisaged that the dose of buspirone could be significantly reduced thereby significantly reducing the quantity of unwanted metabolites and the incidence or severity of side effects whilst still achieving the desired levels of buspirone in plasma and
10 hence the desired therapeutic effect associated with this compound.

In Table 1, the ratio of the area under the plasma concentration-time curve (AUC) for buspirone and the AUC for 1-PP was 0.211 for the "Buspar" formulation,
15 indicating clearly the extensive metabolism of buspirone when administered in a conventional tablet form. The corresponding AUC ratio for Example 1 in Table 1 was 0.718. This demonstrates that administration in the formulation of Example 1 results in a greater proportion
20 of the administered dose of buspirone being absorbed in the unmetabolised form and, indeed, it is apparent from Figure 2 that metabolism of buspirone occurs more slowly for the formulation of Example 1 since the maximum amount of 1-PP for the formulation of Example 1 is observed
25 about 2 hours later than that for the conventional "Buspar" formulation.

Pharmaceutical compositions of this invention will increase the ratio of the unchanged drug to the main metabolite's area under the plasma concentration-time
30 curve (AUC) by at least 1.5 times and, most preferably, by at least 2 times.

Examples 3 to 11

The following additional fast-dispersing dosage forms may be prepared according to the method of Example
35 1:-

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Example 3

	Ingredient	Weight (mg)	% by wt of composition
5	Purified Water EP/USP*	223.875	89.550
	Buspirone HCl	3.000	1.200
	Gelatin EP/USNF	10.000	4.000
	Mannitol EP/USP	7.500	3.000
	Glycine EP/USP	2.500	1.000
	Banana Flavour	0.625	0.250
	Raspberry Flavour	0.625	0.250
	Aspartame EP/USNF	1.875	0.750
Total		250.000	100.000

*Signifies removed during the lyophilisation process.

15

Example 4

	Ingredient	Weight (mg)	% by wt of composition
20	Purified Water EP/USP*	450.750	90.150
	Buspirone HCl	3.000	0.600
	Gelatin EP/USNF	20.000	4.000
	Mannitol EP/USP	15.000	3.000
	Glycine EP/USP	5.000	1.000
	Mint Flavour	2.500	0.500
	Aspartame EP/USNF	3.750	0.750
	Total	500.000	100.000

*Signifies removed during the lyophilisation process.

Example 5

30

	Ingredient	Weight (mg)	% by wt of composition
35	Purified Water EP/USP*	224.750	89.900
	Flesinoxan HCl	4.000	1.600
	Gelatin EP/USNF	11.250	4.500
	Mannitol EP/USP	7.500	3.000
	Mint Flavour	1.250	0.500
	Aspartame EP/USNF	1.250	0.500
	Total	250.000	100.000

*Signifies removed during the lyophilisation process.

40

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Example 6

	Ingredient	Weight (mg)	% by wt of composition
5	Purified Water EP/USP*	666.875	88.917
	Gepirone HCl	10.000	1.333
	Gelatin EP/USNF	33.750	4.500
	Mannitol EP/USP	26.250	3.500
	Grape Flavour	3.750	0.500
	Raspberry Flavour	3.750	0.500
	Aspartame EP/USNF	5.625	0.750
Total		750.000	100.000

*Signifies removed during the lyophilisation process.

15 Example 7

	Ingredient	Weight (mg)	% by wt of composition
20	Purified Water EP/USP*	448.750	89.750
	Ipsapirone HCl	5.000	1.000
	Gelatin EP/USNF	20.000	4.000
	Mannitol EP/USP	15.000	3.000
	Glycine USP	2.500	0.500
	Citric Acid EP/USP	2.500	0.500
	Liquorice Flavour	3.750	0.750
Total		500.000	100.000

*Signifies removed during the lyophilisation process.

Example 8

	Ingredient	Weight (mg)	% by wt of composition
35	Purified Water EP/USP*	225.625	90.250
	Alnespirone	2.500	1.000
	Gelatin EP/USNF	11.250	4.500
	Mannitol EP/USP	7.500	3.000
	Grapefruit Flavour	1.250	0.500
	Aspartame EP/USNF	1.875	0.750
	Total		250.000

*Signifies removed during the lyophilisation process.

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Example 9

	Ingredient	Weight (mg)	% by wt of composition
5	Purified Water EP/USP*	649.375	86.583
	Sumatriptan Succinate	35.000	4.667
	Gelatin EP/USNF	31.875	4.250
	Mannitol EP/USP	22.500	3.000
	Cherry Flavour	3.750	0.500
10	Aspartame EP/USNF	7.500	1.000
	Total	750.000	100.000

*Signifies removed during the lyophilisation process.

Example 10

	Ingredient	Weight (mg)	% by wt of composition
15	Purified Water EP/USP*	225.000	90.000
	Zolmitriptan	5.000	2.000
	Gelatin EP/USNF	10.000	4.000
20	Mannitol EP/USP	7.500	3.000
	Cherry Flavour	1.250	0.500
	Aspartame EP/USNF	1.250	0.500
	Total	250.000	100.000

25 *Signifies removed during the lyophilisation process.

Example 11

	Ingredient	Weight (mg)	% by wt of composition
30	Purified Water EP/USP*	428.750	85.750
	Oxaflozane	30.000	6.000
	Gelatin EP/USNF	20.000	4.000
	Mannitol EP/USP	15.000	3.000
	Lemon Flavour	2.500	0.500
35	Aspartame EP/USNF	3.750	0.750
	Total	500.000	100.000

*Signifies removed during the lyophilisation process.

CLAIMS

1. A pharmaceutical composition for oral administration comprising a carrier and, as an active ingredient, a 5-HT₁ agonist, characterised in that the composition is formulated to reduce pre-systemic metabolism of said 5-HT₁ agonist.
- 5
- 10 2. A composition according to claim 1 in which the composition is formulated to promote pre-gastric absorption of said 5-HT₁ agonist.
- 15 3. A composition according to claim 1 or claim 2 in which the composition is formulated to promote absorption of said 5-HT₁ agonist through the buccal, sublingual, pharyngeal and/or oesophageal mucous membrane.
- 20 4. A composition according to claim 1 in which the composition is formulated to promote absorption of said 5-HT₁ agonist through the stomach mucous membrane.
- 25 5. A composition according to any one of the preceding claims in which the 5-HT₁ agonist is selected from buspirone, gepirone, ipsapirone, zolospirone, umespirone, alnespirone, enilospirone, WY-48723, SUN-8399, tandospirone, flesinoxan, lesopitron, ebalzotan, adatanserin, LY-228729, F-8910-RS, U-93385, SL-87.0765, FG-5893, S-14506, EMD-56551, HT-90B, F-92502-CN, E-4414, MKC-242, F-12439, BIMT-17, LY-39, SL-88.0338, SR-57746A, LY-175644, A-74283, Bay-r-1531, CGS-12066B, CGP-50281, WAY-100012, 3a,4,4a,6a,7,7a-hexahydro-2-[4-[4-(2-pyrimidinyl)-1-[piperazinyl]butyl]-4,7-ethenocyclobuta[f]-1,2-benzisothiazol-3(2H)-one 1,1-dioxide, cis-7-chloro-10-methoxy-5a 10b-dihydro-3N-n-propyl-6H-indeno[1,2-d]azepine, 1-cyclohexyl-3-[4-[4-(2,3-dihydro-2,2-dimethylbenzofuran-7-yl)-1-piperazinyl]-
- 30
- 35

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1-butyl]-2-imidazolidinone, 1-[3-amino-2H-1-benzopyran-2-one-8-yl]piperazine, oxaflozane, RU-5031, CP-93129, naratriptan, avitriptan, rizatriptan, L-694247, IS-159, almotriptan, zolmitriptan, sumatriptan, eletriptan,
5 VML-251, L-0076, ALX-0625, CP-122288, VS-395, L-747201, LY-334370 and salts thereof.

6. A composition according to any one of the preceding claims in which the 5-HT₁ agonist is a 5-HT_{1A} agonist.
10

7. A composition according to claim 6 in which the 5-HT₁ agonist is selected from buspirone, gepirone, ipsapirone, zalospirone, umespirone, alnespirone,
15 enilospirone, WY-48723, SUN-8399, tandospirone and salts thereof.

8. A composition according to claim 7 in which the 5-HT₁ agonist is buspirone or a salt thereof.
20

9. A composition according to any one of the preceding claims in which the active ingredient is present in an amount of from 0.5 to 30% by weight of the composition.
25

10. A composition according to any one of the preceding claims in which the active ingredient is present in an amount of 0.25 to 50 mg.

30 11. A composition according to any one of the preceding claims in which the composition is in the form of a viscous emulsion, syrup or elixir, a sublingual tablet, a suckable or chewable tablet, softgel, lozenge, aqueous or non-aqueous drops or other dosage form
35 designed to release the active ingredient in a controlled manner to saliva or to the buccal, pharyngeal and/or oesophageal mucous membranes, a fast-dispersing dosage

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form designed rapidly to release the active ingredient in the oral cavity, or a bioadherent system.

12. A composition according to claim 11, in which the
5 composition is in the form of a solid fast-dispersing dosage form comprising a network of the active ingredient and a water-soluble or water-dispersible carrier which is inert towards the active ingredient, the network having been obtained by subliming solvent from a composition in the solid state, that composition comprising the active 10 ingredient and a solution of the carrier in a solvent.

13. A composition according to claim 11 or claim 12, in which the composition disintegrates within 1 to 10 15 seconds of being placed in the oral cavity.

14. A pharmaceutical composition for oral administration comprising a carrier, and buspirone as an active ingredient, characterised in that the composition 20 is in the form of a solid fast-dispersing dosage form comprising a network of buspirone and a water-soluble or water-dispersible carrier which is inert towards buspirone, the network having been obtained by subliming solvent from a composition in the solid state, that 25 composition comprising buspirone and a solution of the carrier in a solvent.

15. A pharmaceutical composition for oral administration comprising buspirone in a solid fast-dispersing dosage form which disintegrates within 1 to 10 30 seconds of being placed in the oral cavity.

16. A composition as defined in any one of the preceding claims for use in the treatment of anxiety.

35 17. Use of a composition as defined in any one of claims 1 to 15 for the manufacture of a medicament for the

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treatment of depression.

18. Use of a composition as defined in any one of
claims 1 to 15 for the manufacture of a medicament for
5 the treatment of Attention Deficit Disorder With or
Without Hyperactivity.

19. Use of a composition as defined in any one of
claims 1 to 15 for the manufacture of a medicament for
10 the treatment of panic disorders.

20. Use of a composition as defined in any one of
claims 1 to 15 for the manufacture of a medicament for
use as a memory enhancer.

15 21. Use of a composition as defined in any one of
claims 1 to 15 for the manufacture of a medicament for
the palliative treatment of anxiety neurosis.

20 22. Use of a composition as defined in any one of
claims 1 to 15 for the manufacture of a medicament for
the treatment and/or prophylaxis of incontinence
disorders.

25 23. Use of a composition as defined in any one of
claims 1 to 15 for the manufacture of a medicament for
inducing immunosuppression and/or treating immune
disorders.

30 24. Use of a composition as defined in any one of
claims 1 to 15 for the manufacture of a medicament for
the treatment of sleep apnoea and/or related respiratory
disorders.

35 25. Use of a composition as defined in any one of
claims 1 to 15 for the manufacture of a medicament for
the treatment of substance addiction.

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26. Use of a composition as defined in any one of claims 1 to 15 for the manufacture of a medicament for the treatment of alcohol abuse.
- 5 27. Use of a composition as defined in any one of claims 1 to 15 for the manufacture of a medicament for the alleviation of extrapyramidal motor disorders.
- 10 28. A process for preparing a pharmaceutical composition according to any one of claims 1 to 16 which comprises bringing a carrier into association with said active ingredient.
- 15 29. Use of a fast-dispersing dosage form designed to release active ingredient rapidly in the oral cavity to deliver a 5-HT₁ agonist.

Figure 1: Mean Plasma Buspirone Levels (ng/ml)

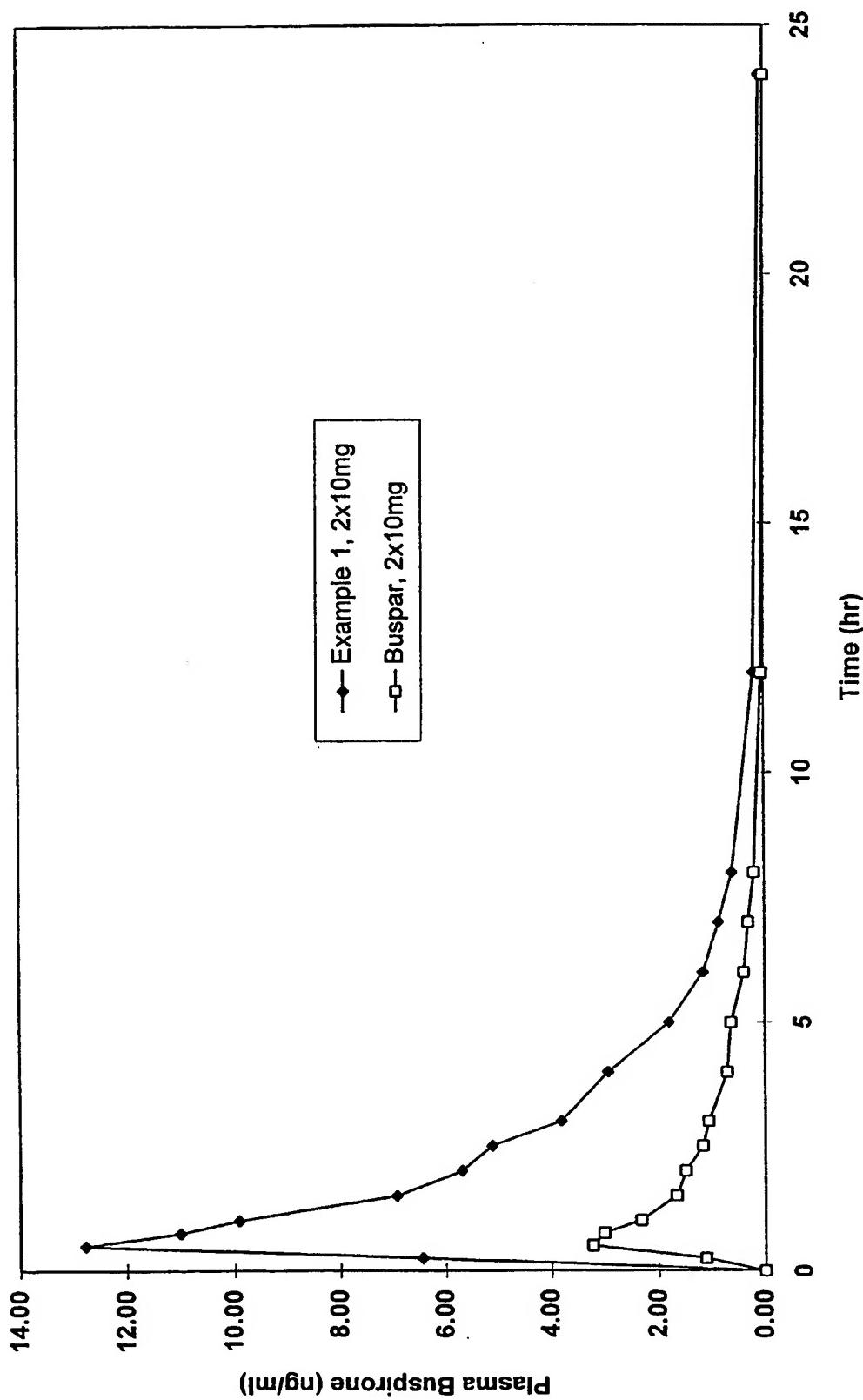
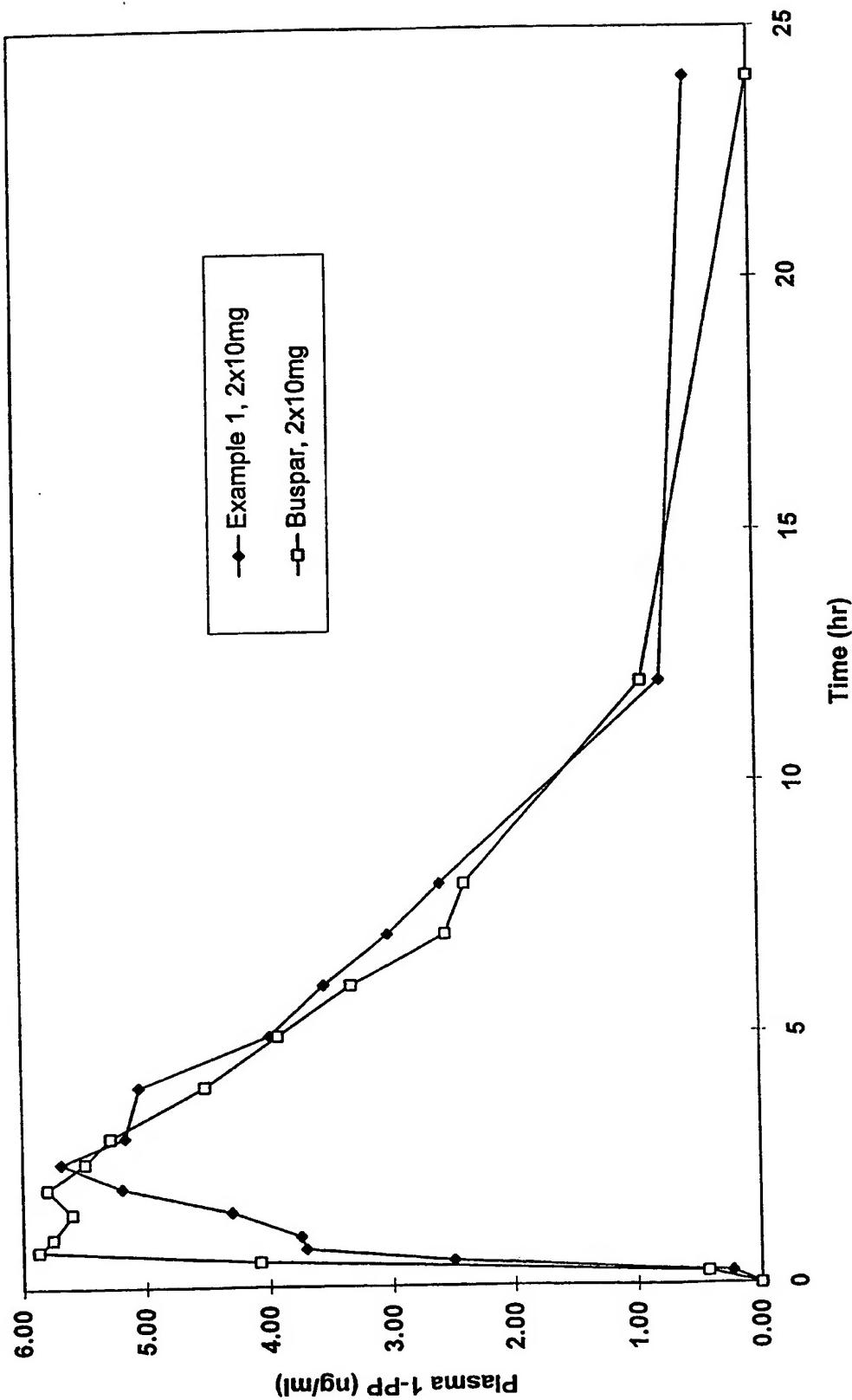


Figure 2: Mean Plasma 1-PP Levels (ng/ml)



INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/00885

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 6	A61K31/505	A61K31/445	A61K31/435	A61K31/495	A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 0, no. 0 & JP 63 250318 A (FUJIMOTO SEIYAKU KK), 18 October 1988 see abstract ---	1-3,5-8, 11,28
X	US 5 246 710 A (AYER) 21 September 1993 * whole document, especially column 3 lines 1-50, examples 9 and 10 and claims * ---	1-3,5-7, 11,16, 17,28
X	US 5 246 711 A (AYER) 21 September 1993 see claim 1 see examples 9,10 ---	1-3,5-7, 11,16, 17,28
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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- "&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 98/00885

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 431 922 A (NICKLASSON) 11 July 1995 see the whole document ---	1,5-10, 16,17,28
X	EP 0 313 535 A (AKTIEBOLAGET ASTRA) 26 April 1989 see the whole document ---	1,5-10, 16,28
X	EP 0 629 402 A (BAYER) 21 December 1994 see page 2 see page 3, line 1 - line 16 see page 4, line 10 see page 5, line 4 - line 34 see page 16 * claims * ---	1,5-7, 16,17,19
X	EP 0 354 777 A (GLAXO GROUP LIMITED) 14 February 1990 * page 2, lines 14-16, lines 53-54 * * page 3, lines 13-31, lines 56-59 * see page 10 - page 11 ---	1-3,6, 11,28
A	DATABASE WPI Week 9304 Derwent Publications Ltd., London, GB; AN 93-032652 XP002040477 see abstract & JP 04 360 826 A (BAYER YAKUHIN KK) 14 December 1992 see abstract ---	1,5-7,9, 10,28
A	GB 1 548 022 A (J.K. EMERSON GREGORY) 4 July 1979 cited in the application see the whole document ---	12-15
A	EP 0 546 593 A (GLAXO GROUP LIMITED) 16 June 1993 see page 2, line 35 - line 58 see page 3 - column 5 ---	12-15,29
A	US 5 478 572 A (S.T. DAVID) 26 December 1995 see the whole document ---	1,5,6, 11,16
A	US 5 169 638 A (A. DENNIS) 8 December 1992 see column 3, line 17 - line 18 see column 4, line 35 see claims 1,11 ---	1,4-8,28
		-/-

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 98/00885

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ROUGE: "Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery" INT. J. PHARMACEUTICS, vol. 136, no. 1-2, 1996, pages 117-139, XP002040474 see page 129 - page 131, left-hand column ---	4
A	TAY: "The site of gastrointestinal absorption of gepirone in humans" J. CLIN. PHARMACOL., vol. 32, September 1992, pages 827-832, XP002040475 see the whole document ---	4-7
A	YU: "Oral cavity absorption of (R)-8-hydroxy-2-(di-n-propylamino)tetralin and (s)-8-acetyl-2-(di-n-propylamino)tetralin in the rat" J. PHARM. PHARMACOL., vol. 48, no. 1, January 1996, pages 41-45, XP002040476 see abstract * page 44, left column, last 4 lines and right column *	1-3, 6
A	EP 0 220 696 A (BRISTOL-MYERS COMPANY) 6 May 1987 see the whole document ---	16, 19
A	EP 0 276 536 A (BRISTOL-MYERS COMPANY) 3 August 1988 see the whole document ---	20
P, X	WO 98 02186 A (FARMARC NEDERLAND BV ;DYER ALISON MARGARET (ZA); PENKLER LAWRENCE) 22 January 1998 see abstract see page 5, paragraph 2 - page 6, paragraph 4 see page 9, paragraph 4 - page 10, paragraph 2; claims; examples 3,4 ---	1-3, 5, 9-13, 16, 28, 29
X	US 5 288 497 A (STANLEY THEODORE H ET AL) 22 February 1994 see the whole document, in particular claims 1-27, 167, 214 ---	1-3, 5, 9-11, 16, 28
X	US 5 288 498 A (STANLEY THEODORE H ET AL) 22 February 1994 see the whole document, in particular claims 1-14, 154, 200 ---	1-3, 5, 9-11, 16, 28

INTERNATIONAL SEARCH REPORT

i. national Application No PCT/GB 98/00885

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 06842 A (PFIZER LTD ;PFIZER RES & DEV (IE); PFIZER (US); HARDING VALERIE DE) 7 March 1996 see abstract see page 2, line 2 - line 23 see page 9, line 3 - line 20; claims 1,6-16; example 6 ----	1-3,5, 9-13,16, 17,21, 25-29
X	EP 0 749 962 A (LILLY CO ELI) 27 December 1996 see abstract see page 4, line 33 - line 39 see page 66, line 26 - line 46; claims ----	1-3,5, 9-11, 16-28
X	EP 0 705 600 A (LILLY CO ELI) 10 April 1996 see abstract see page 17, line 34 - line 54; claims ----	1-3,5, 9-11,16, 28
X	WO 94 25023 A (PFIZER) 10 November 1994 see abstract see page 3, line 20 - line 29 see page 5, line 1 - line 33; claims ----	1-3,5, 9-11,16, 17,21, 25-28
X	WO 94 14772 A (SMITHKLINE BEECHAM PLC ;BORRETT GARY THOMAS (GB); KITTERINGHAM JOH) 7 July 1994 see abstract see page 8, line 20 - line 22; claims see page 6, line 34 - page 7, line 24 -----	1-3,5, 9-11,16, 28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/00885

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
US 5246710 A	21-09-1993	US	5185158 A		09-02-1993
		US	5330762 A		19-07-1994
		US	5688518 A		18-11-1997
		US	5246711 A		21-09-1993
US 5246711 A	21-09-1993	US	5185158 A		09-02-1993
		US	5330762 A		19-07-1994
		US	5688518 A		18-11-1997
		US	5246710 A		21-09-1993
US 5431922 A	11-07-1995	NONE			
EP 313535 A	26-04-1989	AT	108997 T		15-08-1994
		AU	604585 B		20-12-1990
		AU	2623688 A		23-05-1989
		CY	1814 A		20-10-1995
		DE	3850844 D		01-09-1994
		DE	3850844 T		08-12-1994
		DK	294489 A		15-06-1989
		ES	2056955 T		16-10-1994
		FI	893017 A		20-06-1989
		HK	21295 A		24-02-1995
		IE	64705 B		23-08-1995
		JP	2501744 T		14-06-1990
		JP	2674170 B		12-11-1997
		KR	9704906 B		08-04-1997
		MX	9203372 A		01-09-1992
		PT	88820 B		29-01-1993
		WO	8903676 A		05-05-1989
		SG	144094 G		13-01-1995
EP 629402 A	21-12-1994	DE	4319760 A		22-12-1994
		AU	6345794 A		22-12-1994
		CA	2125620 A		16-12-1994
		CN	1099263 A		01-03-1995
		CZ	9401464 A		18-01-1995
		FI	942803 A		16-12-1994
		HU	70759 A		30-10-1995
		JP	6345649 A		20-12-1994
		NO	942228 A		16-12-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/00885

Patent document cited in search report	Publication date	Patent family member(s)		Publication date	
EP 629402	A	NZ PL SK ZA	260732 A 303822 A 72494 A 9404187 A	27-02-1996 09-01-1995 12-04-1995 08-02-1995	
EP 354777	A	14-02-1990	AU DE DK FI JP PT US	3945589 A 68908040 T 391289 A 893751 A 2091068 A 91417 A,B 5036078 A	15-02-1990 18-11-1993 11-02-1990 11-02-1990 30-03-1990 08-03-1990 30-07-1991
GB 1548022	A	04-07-1979	AU AU BE CA CH CY DE FR HK JP JP JP JP JP JP KE LU NL US ZA	513845 B 2882577 A 859291 A 1083042 A 633717 A 1129 A 2744493 A 2366835 A 58081 A 1446344 C 53044619 A 62050445 B 1509556 C 61118314 A 63052008 B 3171 A 78259 A 7710876 A,B, 4371516 A 7705465 A	08-01-1981 22-03-1979 30-03-1978 05-08-1980 31-12-1982 19-02-1982 13-04-1978 05-05-1978 04-12-1981 30-06-1988 21-04-1978 24-10-1987 26-07-1989 05-06-1986 17-10-1988 18-12-1981 09-06-1978 10-04-1978 01-02-1983 25-04-1979
EP 546593	A	16-06-1993	AU AU BE CA CH DE	666880 B 2746992 A 1005490 A 2081709 A 685536 A 69222006 D	29-02-1996 06-05-1993 10-08-1993 01-05-1993 15-08-1995 09-10-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/00885

Patent document cited in search report	Publication date	Patent family member(s)		Publication date	
EP 546593	A	DE ES FR GB IT JP LU MX NZ US ZA	69222006 T 2106818 T 2683146 A 2262445 A, B 1263253 B 5194188 A 88186 A 9206236 A 244921 A 5425950 A 9208359 A	22-01-1998 16-11-1997 07-05-1993 23-06-1993 05-08-1996 03-08-1993 17-05-1993 01-04-1993 27-04-1995 20-06-1995 13-08-1993	
US 5478572	A	26-12-1995	AU CN CZ EP FI HU JP NO NZ PL SG ZA	3043895 A 1128142 A 9502275 A 0700680 A 954154 A 73182 A 8183736 A 953212 A 272855 A 310298 A 30436 A 9507144 A	21-03-1996 07-08-1996 13-03-1996 13-03-1996 07-03-1996 28-06-1996 16-07-1996 07-03-1996 26-05-1997 18-03-1996 01-06-1996 26-03-1996
US 5169638	A	08-12-1992	AT AU AU CA DE DE DK EP ES FI JP MX NZ ZA	161171 T 660193 B 2716792 A 2081070 A 69223588 D 69223588 T 539059 T 0539059 A 2109986 T 924831 A 5194195 A 9205920 A 244517 A 9207433 A	15-01-1998 15-06-1995 29-04-1993 24-04-1993 29-01-1998 25-06-1998 26-01-1998 28-04-1993 01-02-1998 24-04-1993 03-08-1993 01-06-1993 26-10-1994 07-04-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/00885

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
EP 220696	A	06-05-1987		US 4634703 A AU 592121 B AU 6424586 A CY 1786 A DE 3688038 A ES 2053429 T GR 3007393 T HK 87094 A JP 1939806 C JP 6067841 B JP 62111924 A	06-01-1987 04-01-1990 30-04-1987 20-10-1995 22-04-1993 01-08-1994 30-07-1993 02-09-1994 09-06-1995 31-08-1994 22-05-1987
EP 276536	A	03-08-1988		US 4687772 A DE 3780618 A EP 0276543 A JP 1723033 C JP 4005648 B JP 63101324 A	18-08-1987 27-08-1992 03-08-1988 24-12-1992 03-02-1992 06-05-1988
WO 9802186	A	22-01-1998		AU 3455197 A AU 3455297 A WO 9802187 A	09-02-1998 09-02-1998 22-01-1998
US 5288497	A	22-02-1994		CA 1338978 A US 4671953 A AT 129148 T AU 668004 B AU 5521894 A AU 645265 B AU 6287790 A CA 2066423 A DE 69023143 D DE 69023143 T DK 490916 T EP 0490916 A EP 0630647 A ES 2077686 T JP 2717024 B JP 5503917 T WO 9103237 A	11-03-1997 09-06-1987 15-11-1995 18-04-1996 28-04-1994 13-01-1994 08-04-1991 06-03-1991 23-11-1995 28-03-1996 04-03-1996 24-06-1992 28-12-1994 01-12-1995 18-02-1998 24-06-1993 21-03-1991

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/00885

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5288497 A		US 5783207 A		21-07-1998
		US 5785989 A		28-07-1998
		AT 116131 T		15-01-1995
		CA 1271421 A		10-07-1990
		CA 1339190 A		29-07-1997
		DE 3650189 D		09-02-1995
		DE 3650189 T		04-05-1995
		EP 0200490 A		05-11-1986
		EP 0487520 A		03-06-1992
		EP 0490891 A		24-06-1992
		EP 0404205 A		27-12-1990
		US 4863737 A		05-09-1989
		US 4885173 A		05-12-1989
		WO 9103099 A		07-03-1991
		WO 9103234 A		21-03-1991
		US 5484602 A		16-01-1996
		US 5132114 A		21-07-1992
		US 5122127 A		16-06-1992
		US 5288498 A		22-02-1994
US 5288498 A	22-02-1994	CA 1338978 A		11-03-1997
		US 4671953 A		09-06-1987
		AT 138562 T		15-06-1996
		AU 642664 B		28-10-1993
		AU 6337190 A		08-04-1991
		CA 2066403 A		06-03-1991
		DE 69027216 D		04-07-1996
		DE 69027216 T		17-10-1996
		DK 490944 T		21-10-1996
		EP 0490944 A		24-06-1992
		ES 2089027 T		01-10-1996
		JP 2749198 B		13-05-1998
		JP 5500058 T		14-01-1993
		WO 9103236 A		21-03-1991
		AT 116131 T		15-01-1995
		CA 1271421 A		10-07-1990
		CA 1339190 A		29-07-1997
		DE 3650189 D		09-02-1995
		DE 3650189 T		04-05-1995
		EP 0200490 A		05-11-1986

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/00885

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5288498 A		EP 0487520 A		03-06-1992
		EP 0490891 A		24-06-1992
		EP 0404205 A		27-12-1990
		US 4863737 A		05-09-1989
		US 4885173 A		05-12-1989
		WO 9103099 A		07-03-1991
		WO 9103234 A		21-03-1991
		US 5484602 A		16-01-1996
		US 5132114 A		21-07-1992
		US 5122127 A		16-06-1992
		US 5288497 A		22-02-1994
		US 5783207 A		21-07-1998
		US 5785989 A		28-07-1998

WO 9606842 A	07-03-1996	AP 576 A		20-03-1997
		AT 163182 T		15-02-1998
		AU 691005 B		07-05-1998
		AU 2735295 A		22-03-1996
		BG 101250 A		30-09-1997
		BR 9503812 A		16-04-1996
		CA 2198599 A		07-03-1996
		DE 69501620 D		19-03-1998
		DE 69501620 T		02-07-1998
		DK 776323 T		30-03-1998
		EP 0776323 A		04-06-1997
		ES 2112650 T		01-04-1998
		FI 970800 A		26-02-1997
		HR 950460 A		31-08-1997
		HU 77310 A		30-03-1998
		JP 9512283 T		09-12-1997
		LV 11800 A		20-06-1997
		LV 11800 B		20-10-1997
		NO 970861 A		26-02-1997
		PL 318319 A		09-06-1997
		SI 9520091 A		28-02-1998

EP 0749962 A	27-12-1996	NONE		

EP 0705600 A	10-04-1996	US 5698571 A		16-12-1997
		AU 688168 B		05-03-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/00885

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0705600	A	AU 3999695 A CA 2159767 A CZ 9700930 A JP 8208516 A NO 971487 A WO 9611006 A		02-05-1996 06-04-1996 17-09-1997 13-08-1996 02-04-1997 18-04-1996
WO 9425023	A 10-11-1994	AP 486 A AU 689469 B AU 6436094 A BG 100093 A BR 9406435 A CA 2161533 A CN 1121689 A CZ 9502802 A EP 0696194 A HU 73670 A JP 8504829 T NO 954287 A PL 311266 A SG 43951 A SK 133295 A US 5545644 A US 5559129 A US 5559246 A US 5578612 A US 5607951 A ZA 9402805 A		16-04-1996 02-04-1998 21-11-1994 30-04-1996 09-01-1996 10-11-1994 01-05-1996 17-04-1996 14-02-1996 30-09-1996 28-05-1996 26-10-1995 05-02-1996 14-11-1997 08-01-1997 13-08-1996 24-09-1996 24-09-1996 26-11-1996 04-03-1997 23-10-1995
WO 9414772	A 07-07-1994	AU 2851797 A AU 688748 B AU 5814594 A CA 2152630 A CN 1095712 A EP 0674621 A JP 8504790 T MX 9400035 A NZ 259363 A NZ 299232 A US 5618947 A		16-10-1997 19-03-1998 19-07-1994 07-07-1994 30-11-1994 04-10-1995 21-05-1996 29-07-1994 20-12-1996 24-06-1997 08-04-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/00885

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9414772 A		US 5650426 A ZA 9309457 A	22-07-1997 19-06-1995